THE SYNTHESIS OF DIHYDROSPHINGOSINE

BY

JANET LOIS CROSBY

B.S., Iowa State College, 1945

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE COLLEGE OF THE
UNIVERSITY OF ILLINOIS, 1948

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THE SYNTHESIS OF DIHYDROSPHINGOSINE

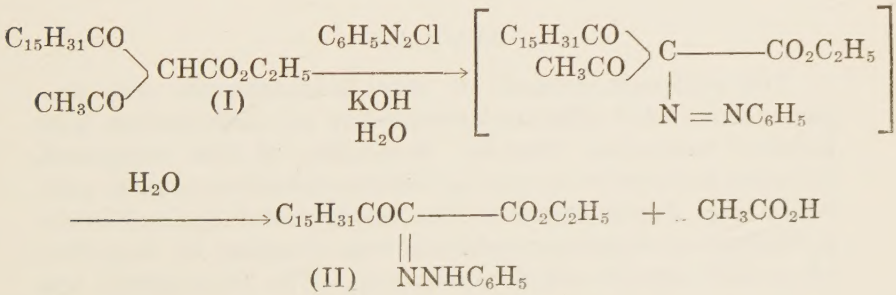
Introduction

Sphingosine and dihydrosphingosine are complex aliphatic bases found in the hydrolysates of certain lipids from brain and spinal cord. Degradation studies carried out in this laboratory (1) recently have established that these bases are 1,3-dihydroxy-2-aminooctadecene-4 and 1,3-dihydroxy-2-aminooctadecane respectively. The present investigation was undertaken in order to provide the final proof of structure of these compounds.

In studies on the reduction of esters of amino and amino-hydroxy acids carried out in this laboratory (2), the methyl esters of DL-threonine and DL-allothreonine were reduced smoothly in the presence of Raney nickel to 1,3-dihydroxy-2-aminobutane. 2-Aminooctadecanol, *dl*-sphingine, was obtained by reduction of methyl α-aminostearate. In view of these results the reduction of methyl α-amino-β-hydroxystearate should lead to the desired aminoglycol. Since Levene (3) has reported that no racemization occurred during the reduction of the esters of optically active amino acids, it should be possible by this method to prepare all four of the optically active isomers of 1,3-dihydroxy-2-aminooctadecane by reducing separately the corresponding esters of the four isomeric amino-hydroxystearic acids.

Discussion of Results

Ethyl palmitoylacetoacetate (I) was condensed with benzene diazonium chloride in cold aqueous potassium hydroxide solution.



From the reaction mixture a yellow crystalline solid could be obtained which analyzed correctly for ethyl α-phenylhydrazono-β-ketostearate (II.) Reduction of this solid (or the crude oily condensation product) with Raney nickel and hydrogen, followed by hydrolysis, yielded α-amino-β-hydroxystearic acid. Esterification with methanol and dry hydrogen chloride produced methyl α-amino-β-hydroxystearate hydrochloride which gave correct analytical results.

The free ester was prepared and reduced with Raney nickel and hydrogen. Benzoylation of the product in dry pyridine yielded a white crystalline solid which gave correct analytical results for 1,3-dihydroxy-2-aminooctadecane. This product represents one of the two possible racemic forms of the aminoglycol, one of the four optically active forms of which is dihydrosphingosine. No evidence was obtained, however, to indicate whether dihydrosphingosine is a constituent of the racemate obtained.

A study was made of the benzoylation of α-aminostearic acid and α-amino-β-hydroxystearic acid under a variety of conditions. The reaction failed in aqueous solution due to the insolubility of these long chain amino acids in aqueous alkali. With aqueous methanol as the solvent 50 per cent yields were obtained from α-aminostearic acid, but results were still unsatisfactory with the aminohydroxy acid. A more satisfactory procedure was afforded by benzoylation of the esters in pyridine. Mild alkaline hydrolysis of the N-benzoyl esters yielded the corresponding N-benzoyl acids.

Summary

The α-phenylhydrazone of ethyl β-ketostearate was prepared from ethyl palmitoylacetoacetate by condensation with benzene diazonium chloride. Reduction of this compound, followed by hydrolysis, yielded α-amino-β-hydroxystearic acid, which was characterized as the methyl ester hydrochloride. 1,3-Dihydroxy-2-aminooctadecane was obtained by reduction of methyl α-amino-β-hydroxystearate. The aminoglycol was

characterized as the tribenzoyl derivative. The compound obtained represents one of the two possible racemic forms of the aminoglycol, one of the four optically active forms of which is dihydrosphingosine.

Benzoyl-α-aminostearic acid and α-benzoylamino-β-hydroxystearic acid were best prepared by benzoylating the corresponding esters in pyridine followed by mild alkaline hydrolysis.

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VITA

The author was born June 1, 1923 in Chicago, Illinois. She was graduated from Hyde Park High School, Chicago in June, 1941 and entered Iowa State College the following September. During her third year at Iowa State College she held a Lane-Wells Scholarship. She received the degree of Bachelor of Science in June, 1945. From July through September, 1945 she was employed by the Sherwin-Williams Company, Kensington, Illinois as a Junior Chemist. She entered the graduate school at the University of Illinois in October, 1945, where she served as a half-time Assistant in Chemistry from October, 1945 to June, 1946. From July, 1946 to August, 1947 she held a Special Research Fellowship granted to the University by the Upjohn Pharmaceutical Company. During her third year (September, 1947 to June, 1948) she received a University Fellowship. From June to August, 1948 she again held an Upjohn Fellowship. She is a member of Iota Sigma Pi, Phi Kappa Phi, and Sigma Xi.

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